Diagnosing, managing and preventing anaphylaxis

European Acad Allergy; Clinical Immunology Food Allergy; de Silva, Debra; Singh, Chris; Muraro, Antonella; Worm, Margitta; Alviani, Cherry; Cardona, Victoria; DunnGlvin, Audrey; Garvey, Lene Heise

Published in:
Allergy

DOI:
10.1111/all.14580

Received: 15 June 2020 | Revised: 13 August 2020 | Accepted: 15 August 2020

DOI: 10.1111/all.14580

ORIGINAL ARTICLE

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

Diagnosing, managing and preventing anaphylaxis: Systematic review

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Funding information
European Academy of Allergy and Clinical Immunology

Abstract

Background: This systematic review used the GRADE approach to compile evidence to inform the European Academy of Allergy and Clinical Immunology's (EAACI) anaphylaxis guideline.

Methods: We searched five bibliographic databases from 1946 to 20 April 2020 for studies about the diagnosis, management and prevention of anaphylaxis. We included 50 studies with 18 449 participants: 29 randomized controlled trials, seven controlled clinical trials, seven consecutive case series and seven case-control studies. Findings were summarized narratively because studies were too heterogeneous to conduct meta-analysis.

Results: It is unclear whether the NIAID/FAAN criteria or Brighton case definition are valid for immediately diagnosing anaphylaxis due to the very low certainty of evidence. There was also insufficient evidence about the impact of most anaphylaxis management and prevention strategies. Adrenaline is regularly used for first-line emergency management of anaphylaxis but little robust research has assessed its effectiveness. Newer models of adrenaline autoinjectors may slightly increase the proportion of people correctly using the devices and reduce time to administration. Face-to-face training for laypeople may slightly improve anaphylaxis knowledge and competence in using autoinjectors. We searched for but found little or no comparative effectiveness evidence about strategies such as fluid replacement, oxygen, glucocorticosteroids, methylxanthines, bronchodilators, management plans, food labels, drug labels and similar.

Conclusions: Anaphylaxis is a potentially life-threatening condition but, due to practical and ethical challenges, there is a paucity of robust evidence about how to diagnose and manage it.

KEYWORDS
adrenaline, anaphylaxis, diagnosis, epinephrine, management, prevention

1 | INTRODUCTION

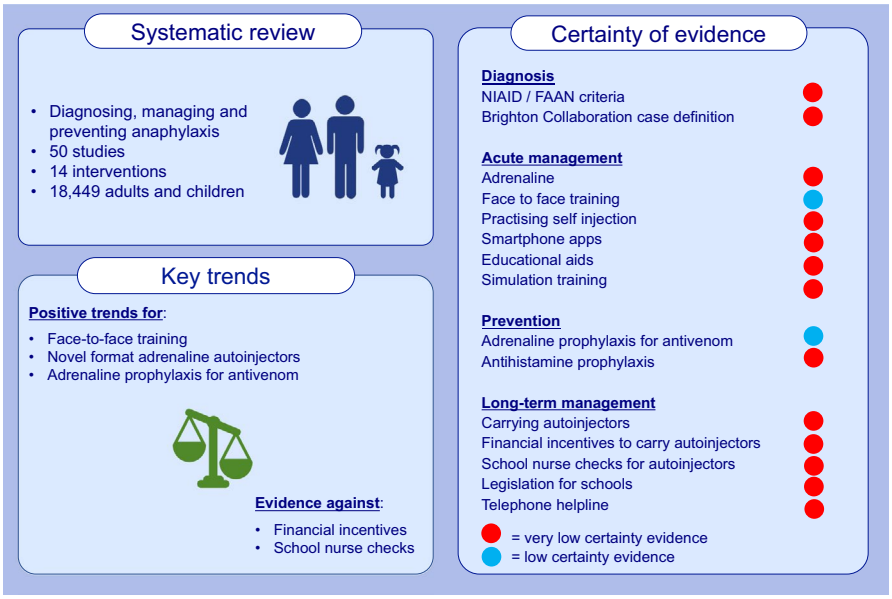
1.1 | Rationale

Anaphylaxis is a severe and potentially life-threatening allergic reaction that all professionals working in healthcare and education should be able to help recognize, manage and prevent. In Europe, about one in 300 people will experience anaphylaxis at some time in their lives.[1] The number of emergency department visits and hospitalizations associated with anaphylaxis is increasing.[2]

Rapid and effective care has an important role in keeping the rate of deaths low,[3] but delayed or ineffective diagnosis and treatment is associated with unnecessary social, psychological and health burden as well as extra costs.[4] Patients, families, health professionals and teachers need to remain up-to-date about ways to diagnose, manage and prevent anaphylaxis, particularly as potential triggers such as food allergy and medication use rise.[5]

In 2014, the European Academy of Allergy and Clinical Immunology (EAACI) released guidelines for managing anaphylaxis.[6] Since that time, new research has been published and the EAACI guideline is being updated. This manuscript describes a systematic review to support the guideline.

A number of other systematic reviews have examined anaphylaxis.[7-14] However, none provide the broad, up-to-date review that is required to inform and update the EAACI guideline. A recent systematic review for an American Practice Parameter contains useful



GRAPHICAL ABSTRACT

Systematic review of 50 studies with 18 449 participants found: Newer/modified models of adrenaline autoinjectors may slightly increase the proportion of people correctly using the devices. Face-to-face training probably improves anaphylaxis knowledge in laypeople. Adrenaline prophylaxis prior to snake bite anti-venom may reduce anaphylaxis.

information about the risk factors for biphasic anaphylaxis and the prophylactic use of glucocorticoids and antihistamine premedication.[15] However, EAACI's guideline will cover a much wider range of interventions to diagnose, treat and manage anaphylaxis, and as such available reviews alone are not sufficient to inform the new guideline.

1.2 | Objectives

This systematic review focuses on three questions:

1. What is the effectiveness of any approach for the immediate diagnosis (intervention) of anaphylaxis (outcome) in children and adults (population) compared with expert panel consensus or any other approach (comparator)?
2. What is the effectiveness of any approach for the emergency management (intervention) of anaphylaxis (outcome) in the community or in hospital in children and adults (population) compared to any other intervention, placebo or no intervention (comparator)?
3. What is the effectiveness of any approach (intervention) for the prevention or long-term management of anaphylaxis (outcome) in children and adults (population) compared to any other intervention, placebo or no intervention (comparator)?

2 | METHODS

The review was undertaken by a task force representing allergists, anaesthetists, emergency medicine clinicians, paediatricians, paramedics, pharmacists, primary care doctors, psychologists, nurses, other clinicians, patient representatives, teachers and methodologists from seven countries.

The review protocol is registered with the International Prospective Register of Systematic Reviews so the methods are only briefly described here (PROSPERO registration: CRD42019159739).[16]

2.1 | Eligibility criteria

Studies were eligible for the review if they included:

- *Population*: children (aged under 18 years) and/or adults (18+ years) with or without a history of anaphylaxis.
- *Intervention*: any intervention to immediately diagnose at emergency presentation, manage or prevent anaphylaxis in the community or hospital. Studies related to immunotherapy were excluded as these are covered in other EAACI guidelines.[17]
- *Comparator*: any comparator, including placebo, no intervention or any intervention or combination of interventions.
- *Outcomes*: anaphylaxis incidence, sensitivity and specificity of diagnostic approaches, mortality or near fatal incidents, hospital admissions, quality of life and other preset outcomes.
- *Study types*: full publications of randomized controlled trials (hereafter trials), controlled clinical trials, controlled before-and-after studies and case-control studies in humans and, in the case of diagnosis and adrenaline (epinephrine) only, consecutive case series with a minimum of 20 participants. There were no language or geographical restrictions.
- *Timeframe*: published from 1946 to 20 April 2020.

The task force selected the review questions following a prioritization process that included canvassing people at risk of anaphylaxis, teachers, healthcare professionals, policy makers and other stakeholders about their priorities. No industry representatives or funders were involved in the prioritization. The questions focused on the effectiveness of any intervention to diagnose, manage or prevent anaphylaxis. Previous reviews have identified limited trials about such interventions[18-20] so we included other comparative designs.

The prioritization process established that stakeholders wanted evidence about the most effective ways to diagnose anaphylaxis in an emergency as well as use adrenaline, amongst other interventions, so the task force explored these topics as part of a broad search strategy which searched for any intervention related to anaphylaxis. Consecutive case series were eligible when studying diagnostic tests and adrenaline because expert advice suggested that it is difficult and potentially unethical to implement more robust designs in these areas. Registry studies, cohort studies and uncontrolled before-and-after studies were excluded in order to focus on the most robust comparative evidence.

2.2 | Study selection and data extraction

An information specialist/methodologist (CS) searched five databases using a search strategy developed with clinicians and patient representatives (see Appendix S1). Two methodologists identified additional references by searching the reference lists of previous reviews, guidelines and identified studies and by seeking recommendations from experts (CS, DdS). Two methodologists independently screened titles and abstracts and the full text of any studies deemed potentially relevant (CS, DdS). Shortlisted studies were rescreened by all clinicians, allied health professionals and patient representatives on the task force (all authors). We excluded studies where it was unclear that the reactions described were anaphylaxis (see Appendix S2). There was 100% inter-rater agreement about the studies included.

Data about study characteristics and outcomes were extracted into a template independently by two methodologists (CS, DdS) and by task force members divided into small topic groups (all authors).

2.3 | Risk of bias in individual studies

Two methodologists independently assessed the risk of bias in individual studies (CS, DdS), as did small groups of task force members (all authors). The Cochrane Risk of Bias tool 2 (ROB2)[21] was used for trials, ROBINS-I[22] for observational studies and QUADAS 2[23] for diagnostic studies. Arbitration was available from two senior clinicians (GR, MW) but there was agreement in the risk of bias assessments.

2.4 | Synthesis of results

The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[24]

Small groups of clinicians and methodologists reviewed studies about each intervention and created evidence profiles (all authors). Authors were not involved in decisions about topics where they had a potential conflict. All taskforce members decided on the conclusions by consensus.

Results were summarized using narrative synthesis. We did not undertake meta-analysis because the minimum criteria for meta-analysis set out in the review protocol were not met.

We used standardized GRADE statements to narratively indicate the effect size and the certainty of the evidence (Table 1).[25] For example, if the certainty of evidence was very low, regardless of effect size, the following terminology was used: "It is unclear whether [intervention] affects [outcomes] because the evidence is very uncertain."

3 | RESULTS

3.1 | Study characteristics

Figure 1 summarizes the number of studies screened and selected. Fifty studies with 18 449 participants were included: 29 randomized trials (58%), seven nonrandomized controlled trials (14%), seven

TABLE 1 Wording conventions used in this article to summarize effect size

	Size of effect			
Certainty of evidence	**None/minor/ not clinically meaningful (0% to 39% relative change)**	**Small (40% to 60% relative change)**	**Medium (61% to 80% relative change)**	**Large (81%+ relative change)**
High	X does not reduce/increase outcome	X reduces/increases outcome slightly	X reduces/increases outcome	X results in a large reduction/increase in outcome
Moderate	X probably does not reduce/increase outcome	X probably reduces/increases outcome slightly	X probably reduces/increases outcome	X probably results in a large reduction/increase in outcome
Low	X may not reduce/increase outcome	X may reduce/increase outcome slightly	X may reduce/increase outcome	X may result in a large reduction/increase in outcome
Very low	It is unclear whether [intervention] has any impact because the certainty of the evidence is very low			

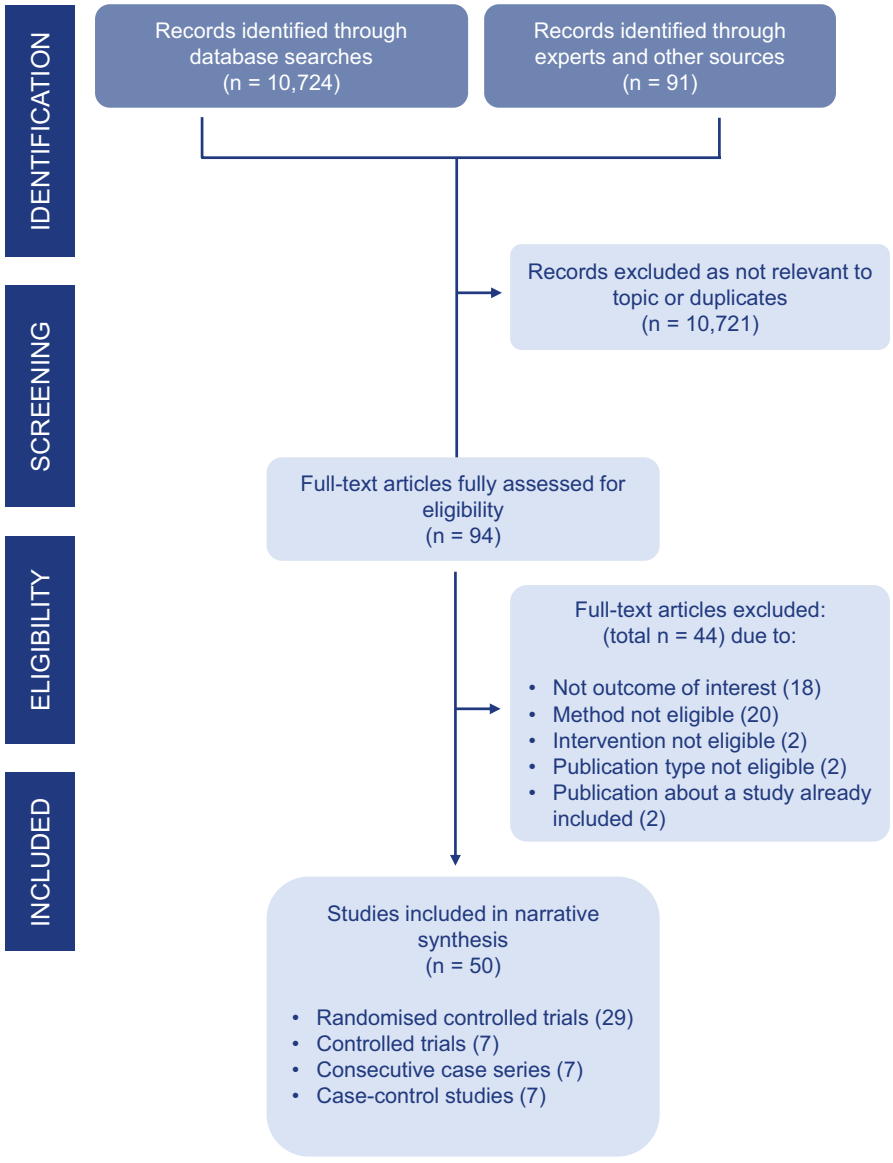


FIGURE 1 PRISMA diagram showing study selection

consecutive case series (14%) and seven case-control studies (14%). Three studies focused on diagnosis, 26 on the acute management of anaphylaxis or the characteristics of adrenaline administration, 9 on education to improve emergency management and 12 on long-term management and prevention.

Overall, 50% of the studies were from North America, 28% from Europe, 12% from Asia, 4% from Australia and 6% from elsewhere. Two thirds (66%) of the studies were published between 2010 and 2020, 18% from 2000 to 2009 and 16% prior to 2000. The online supplement summarizes the individual studies and their risk of bias assessments (see Appendix S3).

More than half of the studies (56%) were at high risk of bias, 40% at moderate risk and 4% at low risk. The GRADE certainty of evidence was generally low or very low (Appendix S4-S8) and was often downgraded due to risk of bias, indirectness and imprecision.

The studies contained multiple outcomes, measured in a range of ways and at a variety of time points. Space does not permit a description of every outcome so only a selection are described here and not all numerical findings and confidence intervals are listed. Appendix S1-S8 describe the outcomes in more detail.

3.2 | Diagnosis of anaphylaxis at presentation

We included three studies with 516 participants about the immediate diagnosis of people presenting with anaphylaxis (as opposed to retrospectively confirming a suspected diagnosis). The task force was interested in immediate diagnosis of anaphylaxis because this may influence the management approach taken. There are a number of diagnostic tools available and the task force wanted to understand whether there was any evidence of effectiveness for these tools. Other approaches such as serum tryptase are not summarized here because they help with subsequent confirmation rather than immediate diagnosis.

TABLE 2 Summary of accuracy of approaches to diagnose anaphylaxis

Intervention	Population	Sensitivity (95% CI)	Specificity (95% CI)	Certainty of evidence	Overall conclusion	Studies (participants)
Second Symposium on the Definition and Management of Anaphylaxis NIAID/FAAN definition (vs review by blinded experts)	Adults and children in emergency department	0.67 (0.46 to 0.75)	0.70 (0.59 to 0.80)	Very low	Unknown accuracy	1 case-control (n = 128)[28]
		0.97 (0.89 to 0.99)	0.82 (0.76 to 0.88)	Very low	Unknown accuracy	1 case-control study (n = 214) [27]
		0.95 (0.85 to 0.99)	0.71 (0.61 to 0.79)	Very low	Unknown accuracy	1 case series (n = 174)[26]
Brighton Collaboration case definition (vs physician diagnosis in the emergency department recorded in case notes)	Adults and children in emergency department	0.68 (0.54 to 0.80)	0.91 (0.80 to 0.96)	Very low	Unknown accuracy	1 case-control (n = 128)[28]

Abbreviation: CI, confidence interval.

The National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria aim to define anaphylaxis for research and clinical purposes. It is unclear whether these criteria help to diagnose anaphylaxis because the certainty of evidence is very low, but there are positive trends (Appendix S4a and Table 2).

Sensitivity is an important indicator of the accuracy of criteria for the immediate diagnosis of anaphylaxis. The NIAID/FAAN criteria may be highly sensitive, but less specific. There were three eligible studies in adults and children, which compared the NIAID/FAAN criteria to a gold standard of blinded physician review or physician diagnosis recorded in notes. One consecutive case series found that the NIAID/FAAN criteria had sensitivity of 0.95 (95% confidence interval (CI) 0.85 to 0.99) and specificity of 0.71 (95% CI 0.61 to 0.79, very low certainty).[26] A case-control study found sensitivity of 97% (95% CI 89% to 99%) and specificity of 82% (95% CI 76% to 88%, very low certainty).[27] Another case-control study found sensitivity of 0.67 (95% CI 0.46 to 0.75) and specificity of 0.70 (0.59 to 0.80, very low certainty).[28]

The Brighton Collaboration case definition is designed for standardizing adverse events following immunizations. It includes many different adverse effects to vaccines, not solely anaphylaxis. It is unclear whether this definition helps to diagnose anaphylaxis because the certainty of evidence is very low (Appendix S4b). One case-control study found that compared to a gold standard of physician diagnosis recorded in notes, this definition had sensitivity of 0.68 (95% CI 0.54 to 0.80) and specificity of 0.91 (95% CI 0.80 to 0.96) in children and adults (very low certainty).[28]

3.3 | Acute management of anaphylaxis

We identified 26 studies with 3,645 participants about the emergency management of anaphylaxis, including characteristics of adrenaline administration.

3.3.1 | Adrenaline

Adrenaline is commonly used for the acute management of anaphylaxis. A number of reviews have examined the efficacy of adrenaline,[29] but these mainly reported studies at high risk of bias. Our review only included comparative studies or consecutive case series with at least 20 participants and we identified no eligible studies comparing adrenaline versus no adrenaline in terms of mortality or most other outcomes. Two case-control studies reported on biphasic reactions in children, but it is unclear whether adrenaline prevents biphasic anaphylactic reactions because the certainty of evidence is very low. One study found a non-statistically significant reduction of 9% and the other a significant reduction of 18% (odds ratio (OR) 0.08, 95% CI 0.014 to 0.43, see Table 3and Appendix S5a).[30,31]

TABLE 3 Impact of adrenaline in the acute management of anaphylaxis

Outcomes	Population	Absolute effect	Relative effect (95% CI)	Certainty of effect	Overall conclusion	Studies (participants)
Biphasic reactions associated with adrenaline	Children	Range 9% ($P > .05$) to 18% ($P < .05$) reduction	OR 0.08 from one study (0.014 to 0.43)	Very low	Unknown impact	2 case-control (n = 269)[30,31]
Biphasic reactions associated with adrenaline administered within 30 minutes of onset	Adults and children	23% reduction ($P < .05$)	OR 3.39 (1.13 to 10.18)	Very Low	Unknown impact	1 case-control (n = 430)[33]
Hospital admissions associated with adrenaline administered before vs at ED	Children	26% reduction if administered before ED ($P < .05$)	OR 0.25 (0.10 to 0.62)	Very Low	Unknown impact	1 case-control (n = 384)[32]
Admission to ICU associated with adrenaline administered before vs at ED	Children	0%	-	Very low	Unknown impact	1 case-control (n = 384)[32]
Overdose associated with intravenous bolus compared to intramuscular adrenaline	Adults and children	13% increase ($P < .05$)	OR 61.3 (7.5 to infinity)	Very low	Unknown impact	1 case series (n = 301)[38]
Cardiovascular events associated with intravenous bolus compared to intramuscular adrenaline	Adults and children	8% increase ($P < .05$)	OR 7.5 (1.6 to 35.3)	Very low	Unknown impact	1 case series (n = 301)[38]

Abbreviations: OR, odds ratio. CI, confidence interval. ED, emergency department.

3.3.2 | Timing of adrenaline administration

The most effective timing of adrenaline administration is unknown because the certainty of evidence is very low (Appendix S5b). One case-control study in children found that administering adrenaline before hospital arrival reduced admissions by 26% compared to administration in the emergency department. There was no reduction in ICU admissions (very low certainty, see Table 3).[32] One consecutive case series in children and adults found that administering adrenaline within 30 minutes of symptom onset reduced the incidence of biphasic reactions by 23% (OR 3.39, 95% CI 1.13 to 10.18, very low certainty).[33] Studies did not report on mortality.

3.3.3 | Adrenaline administration route

It is unclear whether different adrenaline administration routes affect outcomes because the certainty of evidence is very low.

We identified two randomized trials and two nonrandomized trials about adrenaline inhalation as the primary route of administration; three in adults and one in children. Most studies found that inhalation did not deliver a therapeutically appropriate dose of adrenaline or reduce adverse effects compared to intramuscular or subcutaneous injection or placebo (very low certainty, Appendix S5c).[34-37]

One consecutive case series in children and adults found that intravenous bolus administration was associated with a 13% increase in the incidence of adrenaline overdose (OR 61.3, 95% CI 7.5 to infinity) and an 8% increase in the incidence of cardiovascular events compared with intramuscular administration (OR 7.5, 95% CI, 1.6 to 35.3, very low certainty, Appendix S5d and Table 3).[38]

Two trials compared intramuscular versus subcutaneous injection of adrenaline in children and young adults. Intramuscular adrenaline was associated with an absolute increase of mean plasma adrenaline concentration (very low certainty, Appendix S5e).[39,40] However, these studies may be confounded by using different injection sites (thigh versus arm), in addition to different depth of injection.

Adrenaline autoinjectors are not readily available everywhere so alternatives have been tested. One trial with caregivers of children at risk of anaphylaxis tested an adrenaline autoinjector versus a prefilled syringe. 61% more people using a prefilled syringe administered adrenaline without errors compared to those using an autoinjector (OR 4.07, 95% CI 1.29 to 12.86, low certainty, Appendix S5f).[41]

In a nonrandomized trial, health professionals tested an autoinjector or a syringe (not prefilled). Using an autoinjector reduced the time to administration by an average of 70 seconds compared to a syringe and resulted in fewer administration errors (statistically significant, confidence intervals not reported, very low certainty, Appendix S5g).[42]

3.3.4 | Autoinjector models

We identified seven randomized trials, two non-randomized controlled trials and one consecutive case series examining the usability of autoinjectors (Appendix S5h). These encompassed heterogeneous types of autoinjectors and testers, including those at risk of anaphylaxis, healthy volunteers and healthcare professionals.

Some studies explored modifying autoinjectors, such as changing the colour of the safety cap, having an arrow pointing to the injection tip or using voice prompts to guide people through their use. Such modifications may slightly increase the proportion of people correctly using the devices (low certainty)[43-47] and decrease the time taken to administer adrenaline (low certainty).[43,44]

It is unclear whether specific autoinjector models reduce the risk of unintentional injuries because the certainty of evidence is very low. Two trials in adults found that a modified EpiPen was associated with a 18% or 40% reduction in unintentional injuries compared to the "old" EpiPen (very low certainty, statistically significant, confidence intervals not reported).[43,44] Another trial in mothers of children at risk of anaphylaxis found that Anapen was associated with a 14% decrease in unintentional injuries compared to EpiPen (very low certainty, statistically significant, CI not reported).[45]

3.3.5 | Autoinjector needle length

The most effective autoinjector needle length to administer adrenaline is unknown because the certainty of evidence is very low (Appendix S5i). Studies measured the distance between skin and muscle rather than measuring the resulting serum plasma adrenaline concentration or speed of delivery.

Two consecutive case series in adults found that needle length of 14.3 mm or 15.2 mm may be too short to reach the muscle for one to two fifths of women (very low certainty, confidence intervals not reported).[48,49]

Another consecutive case series found that 29% of children under 15 kg may be at risk of having an autoinjector injected into bone with a needle length of 12.7 mm (very low certainty, CI not reported).[50]

3.3.6 | Adrenaline dose for people taking beta blockers

We did not identify robust comparative studies exploring the most effective adrenaline dose.

It is unclear whether taking beta blockers influences the number of adrenaline doses needed because the certainty of evidence is very low (Appendix S5j). A case-control study in adults found that beta blockers were associated with a 3% increase in the likelihood of requiring more than one adrenaline dose (OR 1.26, 95% CI 0.58 to 2.75, very low certainty). This was not statistically significant, even after adjusting for age, sex, allergen and other conditions.[51]

3.3.7 | Adrenaline dose labelling

It is unclear whether the way adrenaline doses are labelled influences outcomes because the certainty of evidence is very low (Appendix S5k). One trial with hospital professionals in a simulated environment found that professionals using ratio labels (1 mL of a 1:1000 solution) had a greater risk of dose errors compared with mass concentration labels (1 mg in 1 mL) (OR 13.4, 95% CI 2.2 to 81.7) and took longer to administer adrenaline (adjusted mean increase 91 seconds, 95% CI 61 to 122 seconds, very low certainty).[52]

3.4 | Education to improve acute management

We identified nine studies with 574 participants about various types of educational interventions to support acute management for people at risk of anaphylaxis, their family, teachers and clinicians.

3.4.1 | Face-to-face training for laypeople

Face-to-face training can take various forms and durations so it is difficult to generalize. Based on the evidence available, a series of face-to-face sessions probably improves knowledge about anaphylaxis in people at risk of anaphylaxis or their carers. One trial found that two three-hour training sessions improved knowledge amongst adults at risk of anaphylaxis and the caregivers of children at risk. This effect remained after three months (moderate certainty, Appendix S6a).[53]

Face-to-face training may slightly improve laypeople's competence in administering adrenaline autoinjectors, but it is difficult to estimate the exact size of the effect due to differences in measurement approaches (Appendix S6a, low certainty). One trial compared face-to-face training with no training[53] and another compared it to video training.[54]

3.4.2 | Practising self-injection

It is unclear whether practising injecting adrenaline using an empty syringe at clinic appointments has any effect on outcomes for people at risk of anaphylaxis because the certainty of evidence is very low. One trial found that adolescents who practised felt more comfortable self-injecting than those who did not practise (very low certainty, Appendix S6b).[55]

3.4.3 | Smartphone app for laypeople

It is unclear whether smartphone educational apps for people at risk of anaphylaxis affect outcomes because the certainty of evidence is very low. In one trial, 38% more laypeople who used a smartphone app to guide them through using an autoinjector undertook all steps correctly compared to those who received standard autoinjector instruction (CI not reported, statistically significant, very low certainty, Appendix S6c).[56]

3.4.4 | Educational aids for health professionals

It is unclear whether prompts or visual aids help health professionals manage anaphylaxis more effectively because the certainty of evidence is very low (Appendix S6d). One trial found that hospital residents who received training on the use of a wallet sized prompt sheet did not improve their knowledge more than controls in nine out of ten topic areas (very low certainty).[57] Another trial found that a visual prompt about the Brighton Collaboration case definition did not improve the accuracy of anaphylaxis diagnosis compared to a journal article containing the full definition (very low certainty).[58] A nonrandomized trial found that a flowchart did not reduce administration errors in a simulation about reactions to contrast media.[59]

3.4.5 | Simulation training

It is unclear whether simulation training for health professionals has any effect on anaphylaxis management because the certainty of evidence is very low. We identified two trials, each using a different approach to simulation with medical students (Appendix S6e). In one trial, simulation-based training did not increase the proportion of medical students who correctly managed anaphylaxis[60] and in the other trial there was a mean improvement of 22% compared to those taught without simulation (very low certainty, CI not reported).[61] Other studies of simulation training are available but these did not meet the inclusion criteria.

3.5 | Medications to prevent anaphylaxis

We identified seven studies with 13 383 participants about adrenaline, corticosteroids and antihistamine to prevent anaphylaxis as a result of reactions to snake bite anti-venom or other medications.

3.5.1 | Prophylactic medications for anti-venom anaphylaxis

Adrenaline prophylaxis prior to snake bite anti-venom may reduce anaphylaxis and not be associated with significant adverse effects,

TABLE 4 Impact of medications to prevent anaphylaxis

Outcomes	Population	Absolute effect	Relative effect (95% CI)	Certainty of effect	Overall conclusion	Studies (participants)
Severe reactions within 1 h of prophylactic adrenaline for snake bite anti-venom	Children and adults	43% reduction ($P < .05$)	Adjusted OR 0.57 (0.43 to 0.75)	Very Low	Unknown impact	1 trial (n = 1007)[63]
Severe reactions within 48 h of prophylactic adrenaline for snake bite anti-venom	Children and adults	Range 8% to 38% reduction ($P < .05$)	RR in one study 0 (0 to 1.3) Adjusted OR in another study 0.62 (0.51 to 0.74)	Low	May reduce	2 trials (n = 1112)[62,63]
Severe reactions within 1 h of prophylactic hydrocortisone for snake bite anti-venom	Children and adults	0.5% increase ($P > .05$)	OR 0.86 (0.60 to 1.24)	Very low	Unknown impact	1 trial (n = 1007)[63]
Moderate and severe reactions within 48 h of prophylactic hydrocortisone for snake bite anti-venom	Children and adults	23% reduction ($P > .05$)	Not reported	Very Low	Unknown impact	1 trial (n = 52)[64]
Moderate and severe reactions within 48 h of prophylactic hydrocortisone plus chlorpheniramine for snake bite anti-venom	Children and adults	23% reduction ($P > .05$)	Not reported	Very low	Unknown impact	1 trial (n = 52)[64]
Severe reactions within 1 h of prophylactic promethazine (antihistamine) for snake bite anti-venom	Children and adults	2.9% reduction ($P > .05$)	OR 0.81 (0.51 to 1.30)	Very low	Unknown impact	1 trial (n = 1007)[63]
Anaphylactic reactions within 24 hours of prophylactic promethazine (antihistamine) for snake bite anti-venom	Children and adults	1% reduction ($P > .05$)	Not reported	Very low	Unknown impact	1 trial (n = 101)[65]

Abbreviations: OR, odds ratio; CI, confidence interval; RR, relative risk.

though it is difficult to generalize as there are various anti-venoms, only a small amount of evidence was identified and there may be unreliability in the findings. Two trials in children and adults in Asia found that low dose prophylactic adrenaline 0.25 mL (1:1000) injected subcutaneously reduced the risk of severe reactions to anti-venom without significant adverse effects, although the outcomes measured, size of the effects and significance of the results varied between studies (see Table 4, low certainty, Appendix S7a).[62,63]

It is unclear whether prophylactic intravenous corticosteroids or histamine receptor blockers reduce anaphylaxis resulting from anti-venom for snake bite because the certainty of evidence is very low. Two trials in children and adults in Asia found that hydrocortisone alone or with chlorpheniramine did not reduce the incidence of moderate to severe reactions (low certainty, Appendix S7b).[63,64]

Two trials in children and adults found that the antihistamine promethazine did not reduce the incidence of anaphylaxis within 24 to 48 h of anti-venom (very low certainty, Appendix S7c).[63,65]

3.5.2 | Antihistamine for plasma substitute and experimental histamine-induced reactions

It is unclear whether prophylactic antihistamine reduces plasma substitute and histamine-induced anaphylaxis because the certainty of evidence is very low (Appendix S7d). One trial about prophylactic antihistamine prior to plasma substitute haemaccel found a 24% reduction in the incidence of anaphylaxis (statistically significant, CI not reported, very low certainty).[66] Another trial of prophylactic antihistamine prior to intravenous histamine infusion found that intramuscular H1 + H2 receptor-antagonist pretreatment reduced reactions (numbers not reported, very low certainty).[67]

3.6 | Long-term management approaches

We identified five studies with 331 participants about long-term management approaches for anaphylaxis.

3.6.1 | Carrying an autoinjector

It is unclear whether carrying an adrenaline autoinjector impacts on the perceived burden of care amongst people at risk of anaphylaxis because the certainty of evidence is very low (Appendix S8a). One trial with people allergic to yellow jacket venom found that carrying an adrenaline autoinjector was associated with a 44% increase in the perceived burden of treatment compared to venom immunotherapy (statistically significant, CI not reported, very low certainty).[68]

We did not identify any eligible studies assessing the most effective number of autoinjectors to prescribe.

3.6.2 | Financial incentives to carry autoinjectors

It is unclear whether providing people at risk of anaphylaxis with financial incentives increases how often they carry autoinjectors because the certainty of evidence is very low (Appendix S8b). One trial in people aged 18 to 30 years found that financial incentives were associated with a 27% mean increase in the proportion of people carrying their autoinjector (statistically significant, CI not reported, very low certainty).[69]

3.6.3 | School nurse checks of carrying autoinjectors

It is unclear whether regular checking by school nurses encourages school students to carry their adrenaline autoinjectors because the certainty of evidence is very low (Appendix S8c). In one non-randomized trial checks by school nurses were associated with an absolute decrease (not improvement) of 15% in the proportion of students carrying autoinjectors (not statistically significant, CI not reported, very low certainty).[70]

3.6.4 | Legislation about school management plans

It is unclear whether legislation requiring schools to have anaphylaxis management plans affects outcomes because the certainty of evidence is very low (Appendix S8d). A case-control study found that legislation improved the consistency of school policies with best practice guidelines (very low certainty) and was associated with a 13% increase in the proportion of school staff scoring 4 out of 4 on observed autoinjector technique (statistically significant, CI not reported, very low certainty).[71]

3.6.5 | Helpline

It is unclear whether telephone helplines improve outcomes for those at risk of anaphylaxis because the certainty of evidence is very low (Appendix S8e). One trial with children and their families found that a telephone helpline was associated with a clinically important improvement on a validated food allergy quality of life scale at 12 months. There was no statistically significant difference in use of health services for allergic events or anaphylaxis (very low certainty).[72]

4 | DISCUSSION

4.1 | Summary of evidence

We found little robust evidence about the most effective strategies to diagnose, manage or prevent anaphylaxis. Although we wanted to include a wide variety of interventions, most of the comparative

studies available were about adrenaline, and even these were largely of low quality or difficult to interpret.

There were only three areas where the certainty of evidence was not "very low." Firstly, newer/ modified models of adrenaline autoinjectors may slightly increase the proportion of people correctly using the devices and reduce the time taken to administer adrenaline. Secondly, face-to-face training probably improves knowledge about anaphylaxis in people at risk of anaphylaxis and their family and may slightly improve laypeople's competence in administering adrenaline autoinjectors. Face-to-face training can be of varying duration and content, but there is little evidence about the most effective type of training. Thirdly, adrenaline prophylaxis prior to snake bite anti-venom may reduce anaphylaxis. However, this evidence comes largely from Asia and may relate to types of anti-venoms that are not commonly used in other parts of the world.

For all other diagnostic and management interventions, the evidence was of too low certainty to draw conclusions. We searched for but found no eligible studies examining treatments such as fluid replacement, oxygen, glucocorticosteroids (apart from for anti-venom), methylxanthines and bronchodilators. Nor was there robust comparative evidence about the effectiveness of food or drug labelling, management plans or other management or prevention approaches.

4.2 | Comparison with previous research

This review differs from previous reviews because it excluded non-consecutive case series, registry and cohort studies and other observational methods at high risk of bias. The rationale was to focus on research designs of higher quality to best inform the EAACI guideline. This means that there are some differences in our findings compared to past reviews. In particular, we found little evidence about the effectiveness of acute management approaches, whereas reviews that have included observational study designs have found trends towards improved health outcomes and fewer hospital admissions when adrenaline is used as first-line treatment.[11,15,73]

Our review differs from the 2020 American Practice Parameter[15] which focused primarily on prophylactic use of glucocorticoids and antihistamine premedication. Our narrower inclusion criteria for study designs aimed to collate the most robust research. This meant that we found few eligible studies about premedication compared to the Practice Parameter. Furthermore immunotherapy studies were not eligible for our review. Another difference is that we included only studies explicitly about anaphylaxis and excluded studies which explored "reactions" whereas the American Practice Parameter included a broader range of reactions. On the other hand, the wider scope of our review means we have explored educational initiatives and non-pharmacological long-term management approaches, which were not covered in the Practice Parameter. Thus, our review complements that undertaken for the Practice Parameter as each had a different focus.

4.3 | Implications for research

This review highlights the need for further research. For example, robust studies are needed to test the feasibility of criteria for immediate diagnosis against gold standard expert review and the value of other approaches such as tryptase measurements to help confirm the diagnosis.

There is a paucity of robust evidence about acute management approaches, but a lack of evidence is not the same as a lack of effect. It may be considered unethical to withhold a potentially life-saving treatment so more creative study designs may be needed to further knowledge in this area. Even amongst commonly used treatments, such as adrenaline, much remains to be learnt including the ideal dosage and delivery mechanism required for adults and children. Robust studies comparing the most effective number of autoinjectors to prescribe would also inform practice.

Long-term management and prevention may help people to identify triggers, minimize the risk of further reactions, learn skills and address psychological consequences. Various educational programmes, smartphone apps and leaflets have been developed, and anaphylaxis management plans and legislation have been implemented in some areas. Randomized trials or quasi-randomized studies would help to understand whether such approaches are worth expanding.

4.4 | Strengths and limitations

This review was conducted by a task force of diverse clinicians, allied health professionals, public representatives, teachers and researchers. This was a strength because it meant that interventions and outcomes were considered on clinical and methodological grounds, with robust checks by multiple experts.

The review provides an up-to-date summary of research, with two thirds of the included studies being published in the past decade. However, it has several limitations. The available evidence is heterogeneous and mostly at moderate or high risk of bias. Meta-analysis was not appropriate because the interventions and outcomes varied greatly and there were too few studies with similar outcomes. A number of studies examined outcomes that may not be the most helpful when seeking to assess effectiveness, such as whether people carry autoinjectors or short-term changes in quality of life. Very few studies reported in detail on mortality, admissions, preferences or resource use. There was also a lack of evidence about emergency management outside hospital.

Not all available interventions are included in the review because data from meta-analyses, registry studies, cohort studies and other non-comparative designs were not included. These designs have often been used to explore the efficacy of approaches such intravenous fluids or to track the value of preventive approaches including food labels, educational interventions and management plans. Our focus on comparative effectiveness research is a limitation as well as a strength because it means that not every intervention tested for

diagnosing, managing or preventing anaphylaxis is included in the review. Some of these interventions may be worthwhile, even though robust comparative research is not yet available.

All research and reviews have the potential to be affected by unconscious bias. This review is no exception. Some of the reviewers have previously researched interventions to diagnose, manage or prevent anaphylaxis, but none of the reviewers have a vested interest in the outcome of this review. Decisions about study eligibility for inclusion were undertaken by reviewers who have never received funding from industry. However, it is important to acknowledge that biases and familiarity can influence the framing and prioritization of reviews and the research upon which they are based. The task force included lower quality evidence about adrenaline administration methods because this is a commonly used management approach and the task force wanted to ascertain what evidence existed to challenge or support this. Even with this lower threshold, the evidence was of limited use.

4.5 | Conclusions

There is low certainty of evidence upon which to suggest the most effective strategies for diagnosing, managing and preventing anaphylaxis. EAACI's forthcoming anaphylaxis guidelines will combine the findings from this review with expert opinion and other evidence to suggest practical implications for health professionals, teachers and families.

ACKNOWLEDGEMENTS

The European Academy of Allergy and Clinical Immunology (EAACI) funded the systematic review to support the development of an anaphylaxis guideline. The funder had no role in the development of the protocol, conduct or write up of the review or decision to publish.

CONFLICT OF INTEREST

Professor de Silva reports a grant to her organisation from EAACI to support the conduct of the study. Dr Singh reports a grant to his organisation from EAACI to support the conduct of the study. Professor Muraro reports grants and personal fees from Aimmune and personal fees from DVB, Mylan, ALK and Nestle outside the submitted work and was past President of EAACI. Professor Worm reports grants and personal fees from ALK, grants from GAP study and personal fees from Aimmune, DBV Technologies, Regeneron Pharmaceuticals, Sanofi Aventis, Leo Pharma, Mylan, ARLA and Nestle outside the submitted work and is WAO co-chair anaphylaxis committee. Dr Alviani has nothing to disclose. Dr Cardona reports personal fees from ALK, Allergopharma, Allergy Therapeutics, Diater, LETI and Thermo Fisher outside the submitted work and SLAAI chair anaphylaxis committee, WAO chair anaphylaxis committee. Dr DunnGalvin reports grants from Aimmune Therapeutics, National Children's Research Centre Ireland, DBV Technologies, SafeFood Ireland and Atlanta Clinical Trials in Food outside the submitted work. Dr Heise Garvey reports personal fees from Novo Nordisk, Merck and Thermo Fisher Scientific outside the submitted work. Dr Riggioni has nothing to disclose. Dr Angier reports BSACI member and Anaphylaxis Campaign scientific board member. Dr Arasi has nothing to disclose. Dr Bellou has nothing to disclose. Dr Beyer reports grants and personal fees from Aimmune, grants and personal fees from ALK, grants and personal fees from Danone, grants and personal fees from DBV, grants and personal fees from Infectopharm, grants and personal fees from Thermo Fisher, grants and personal fees from Hycor, grants from DST Diagnostic, Good Mills, Hipp, VDI, EU, German Research Foundation, BMBF and personal fees from Allergopharma, Bausch & Lomb, Bencard, Jenpharma, Mabylon, Mylan, Nestle, Novartis and Nutricia outside the submitted work. Dr Bijlhout has nothing to disclose. Dr Bilo reports personal fees from ALK, Allergy Therapeutics, Astra, GSK and Sanofi outside the submitted work. Dr Brockow reports personal fees from Thermo Fisher and Meda outside the submitted work. Dr Fernandez-Rivas reports grants from ISCIII (Ministry of Science, Spanish Government), grants and personal fees from Aimmune and personal fees from DBV, Novartis, Schreiber Foods, Diater, GSK, HAL Allergy and Thermo Fisher Scientific outside the submitted work. Professor Halkan reports grants and personal fees from ALK outside the submitted work. Dr Jensen reports personal fees from Norvatis outside the submitted work. Dr Khaleva has nothing to disclose. Dr Michaelis reports grants and personal fees from Danone Nutritica, grants and personal fees from Sanofi and personal fees from Novartis and Allergy Therapeutics outside the submitted work. Dr Oude Elberink reports grants and personal fees from Meda, grants and personal fees from ALK-Abello and grants from Novartis outside the submitted work and is on the Advisory Board of PIMS Epinephrine. Ms Regent reports she is employed by the Anaphylaxis Campaign, UK outside the submitted work. Dr Sanchez reports a personal fees from Aimmune Therapeutics outside the submitted work. Dr Vlieg-Boerstra reports grants and personal fees from Nutricia and personal fees from Mead Johnson, Thermo Fisher and Marfo Food Groups outside the submitted work. Professor Roberts reports he is Editor in Chief Clinical & Experimental Allergy.

AUTHOR CONTRIBUTIONS

All authors conceptualized the work, commented on the work and approved it for submission. DdS and CS searched for studies, extracted data and drafted the review.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: de Silva D, Singh C, Muraro A, et al; European Academy of Allergy and Clinical Immunology Food Allergy and Anaphylaxis Guidelines Group. Diagnosing, managing and preventing anaphylaxis: Systematic review. *Allergy*. 2020;00:1–14. https://doi.org/10.1111/all.14580